## DETAILED ACTION

### *Status of the Claims*

Claims 1-9 are cancelled. Claims 10-29 are pending further prosecution on the merits.

### *Objection*

Claim 1 does not have a period after the sentence. An appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yelle et al. (USPN 6,174,902 B1) in view of Thapa ( Lyophilization of Unit Dose Pharmaceutical Dosage Forms, Drug Development and Industrial Pharmacy, May 2003, Vol. 29, No.5, Pages 595-602, printed pages 1-9).

Yelle et al. teach a process for preparation of a rabeprazole composition that fully encompasses and renders obvious the claimed invention (see abstract).

Yelle et al. teach in column 6 at lines 14-20 that [t] he invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

Solubilization of rabeprazole occurs in water in Example 1 in column 6.

Dissolution of lactose occurs in Example 1 in column 6 at line 39.

Adjustment of the pH would naturally and reasonably occur in order to suitably conduct a process for preparation and therefore hold no patentable weight in view of the claimed invention.

For instance, Yelle et al. teach in column 5 at lines 15-18 that [...]. [s]ince the compound of the present invention is a weak acid and is unstable at low pH salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. [...]. Thus, it is art-known that if the invention is unstable at a low pH, then a pH above 7 is required. It is well-established in the pertinent art of general chemistry that a pH of 1-7 constitutes an acid and from 7-11, a base. Therefore, the limitation in the claim drawn to a pH of the solution to 8-11 is adequately overcome.

The removing of particulates from the preparation is taught in Example 1 in column 6 at line 42 where the material is passed through a 16-mesh sieve to give granules.

Lyophilization of the solution occurs via Yelle et al. in Example 3 which teach that the enteric granules of Example 2 (column 6 at lines 48-60) are produced by coating the granules with the enteric coating composition.

Yelle et al. teach the limitations of claim 12 by disclosing excipients in a formulation. Accordingly, it is well-established in the art that suitable excipients are standard components in pharmaceutical compositions of this nature. Specifically, in Example 1 a carbonate buffer is taught as precipitated calcium carbonate and Example 2 teach magnesium carbonate among other excipients.

Examples 1 and 2 in column 6 contain limitations that are obvious over claims 10-11. Rabeprazole is taught as 30 mg, whereas lactose is taught as 73.4 mg. This standard ratio overcomes the limitations in claims 10-11 drawn to variable weight percentages of the active, the binder (lactose), and other miscellaneous excipients. Accordingly, with the exception of the

active (rabeprazole) and lactose, the excipients listed adequately overcome the components listed in instant claim 12.

Further, the limitation of claim 14 which is drawn to the pharmaceutical composition extemporaneously dissolved in water before administration is made obvious via the Example 2 vignette which clearly teaches the formulation dissolved in *inter alia* water of 0.05 milliliters.

Specifically, it is well-established according to the claimed invention that granules are compacted to make tablets. The granules lyophilized for reconstitution in intravenous preparations contain all the same ingredients as compacted tablets but are in a powdered or granulated form. In view of the teachings of Yelle et al., claim is directly drawn to a reconstitutable mixture that can be dissolved in water for intravenous use. Yelle et al. teach in column 5 at lines 51-65 that:

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

Yelle et al. does not teach the two stages of drying based upon the lyophilization procedure in claims 28 and 29.

Thapa et al. teach that a typical freeze-drying cycle essentially consists of three stages: freezing, primary drying, and secondary drying (page 2, specifically lines 4-8, see Introduction page 1-2).

Specifically, in lines 4-8, claims 28 and 29 are made obvious due to Thapa describing that in the first stage, the material is cooled until frozen. The first stage of claims 28 and 29 disclose a primary drying at a product temperature below -10 C. Thapa et al. further describes the second stage as accomplished under vacuum and by supplying heat to the product, involves the removal of most of the water by sublimation of the ice in the product. Accordingly, the second stage of claims 28 and 29 disclose a secondary drying at a temperature below 25C.

Thus, it would have been *prima facie* obvious to the one of skill at the time of invention to administer a process for preparation of a rabeprazole composition as taught by Yelle et al. with the standard procedure of the lyophilization of pharmaceutical dosage forms as taught by Thapa.

The motivation to administer the process for preparation of rabeprazole as taught by Yelle et al. with the process of lyophilization as taught by Thapa et al. is due to the fact that Yelle et al. teach a therapeutically effective composition comprising rabeprazole. For the purposes of facilitating improved administration, lyophilization is art-known for improved stability of the active substance.

Further, Thapa et al teach that lyophilization is a widely used technique for the stabilization and preservation of heat labile substances and its use in the preservation of microorganisms, foodstuffs, biological products, and pharmaceuticals is well documented (page 1 and 2 under Introduction at lines 1-4. Thus, the limitation drawn to a shelf life of 6 months is

reasonably overcome by the teachings of Thapa et al. The one of skill would readily recognize that via characterization optimization of the lyophilization process that the limitations of claims 28 and 29 could be readily met.

The scope and content of Yelle principally teach the active agent rabeprazole and the essential excipients as disclosed. Yelle et al. teach a method of preparing and a method of use of the rabeprazole formulation. Yelle et al. meets the limitations drawn to specific weight percentages of each component in the formulation. Accordingly, Thapa et al. teach the scope and content of the invention drawn to a typical drying procedure for lyophilization of pharmaceutical.

The difference in Yelle et al. in view of the claimed invention is that lyophilization is not taught specifically as two-stage drying process. However, in the absence of any evidence in the specification delineating a distinct invention based upon the lyophilization process, the lyophilization process of Yelle et al. is obvious over the claimed invention. Due, routine experimentation and the manipulation of the temperature would reasonably duplicate any condition required in the effort to improve the lyophilized product for increased shelf-life and over-all stability for therapeutic administration.

The objective evidence in the application indicating obviousness is the same formulation of rabeprazole of the claimed invention is interchangeable with the formulation and process of Yelle et al. in as far as it would be apparent to one of skill in the pertinent art that many modification, both materials and methods, may be practiced without departing from the purpose and interest of this invention (column 6 at lines 17-20).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

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